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Emergence of copper-mediated formation of C–C Bonds

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Abstract: Copper-catalysed cross coupling reactions have found widespread application in carbon-carbon or carbon-heteroatom bond formation. The non-toxicity, ease of handling and low cost of these versatile complexes make them attractive for the elaboration of new methodologies and for the obtaining of new compounds. We focus on recent methods for the copper-mediated formation of carbon-carbon bonds which will be illustrated by different coupling reactions: cross-dehydrogenative coupling, decarboxylative cross-coupling, Sonogashira- type reaction, Suzuki- type reaction and Negishi- type reaction. Domino reactions and finally more atypical reactions will also be illustrated.

Carine Maaliki received her Ph.D degree in Organometallics from the University of Paul Sabatier in Toulouse in 2012 under the supervision of Prof. R. Chauvin. She, then, moved to The University of Namur for her postdoctoral study with Prof. S. Vincent where she worked on carbohydrate chemistry. Since may 2014, she starts a second postdoctoral stage in the University of Sciences and Technologies of Tours. She focused on medicinal chemistry working on important core of natural products.



Emilie Thiery received her PhD in organic chemistry from the University of Reims Champagne-Ardenne in 2008 under the supervision of Dr Jacques Muzart and Dr Jean Le Bras. She then moved to Prof. S. Vincent's group at the University of Namur where she worked on carbohydrate chemistry. She then went back to France as a Maître de Conférences at the University of François-Rabelais of Tours. Her research interests include organometallic chemistry and development new strategies for the synthesis of heterocycles.



Jérôme Thibonnet, born in 1971 in Joinville (France), received his PhD in 1999 from the University of Tours where he worked on the total synthesis of retinoids under the supervision of Professor Alain Duchêne. After postdoctoral studies in the laboratory of Professor Paul Knochel at the University of Munich, he joined the University of Aix-Marseille III as Ingénieur de Recherche at the laboratory of Professor Maurice Santelli (2000). He became lecturer at the University of Tours in 2003 and he was promoted to full professor in 2009. His research interests include new catalytic reactions toward new synthetic methods, the synthesis of biologically relevant compounds, and synthetic organic materials.



1. Introduction

Carbon-carbon and carbon-heteroatom bonds formation is the key transformation in organic synthesis to set up the carbon backbone of organic molecules. Due to the importance of these bonds, the possibility of finding novel disconnections for the efficient synthesis of organic molecules has driven interest in developing new technologies.^[1] To achieve these transformations, the transition metal catalysts, particularly those derived from the group VIII-X metals, display remarkable efficiency through the reactions of suitable nucleophiles with organic electrophilic partners. These transformations are typically catalysed by palladium or nickel complexes and are referred as “cross-coupling reactions”. These methods have profoundly revolutionized the protocols for the synthesis of organic on both bench-top and industrial scales. They are valuable tools in the synthesis of potential pharmaceuticals, natural products, organic materials, and polymers.^[2] Nowadays, the weak production (figure 1) and the high price (figure 1) of precious metals usually used in catalysis such as palladium, rhodium, or iridium have drawn the chemical’s community’s attention back to alternative processes as copper^[3] or iron^[4] catalysis. Recently, the development of an approach to replace catalytic systems of noble metals (e.g., high cost, low natural abundance, toxic, widely used in automotive, electronic) with nonprecious metals is currently in high demand. With its low cost, high natural abundance, and low toxicity, copper is indeed a particularly appealing alternative, and accordingly, the development of copper-catalysed cross-coupling is undergoing an explosive growth (figure 1).

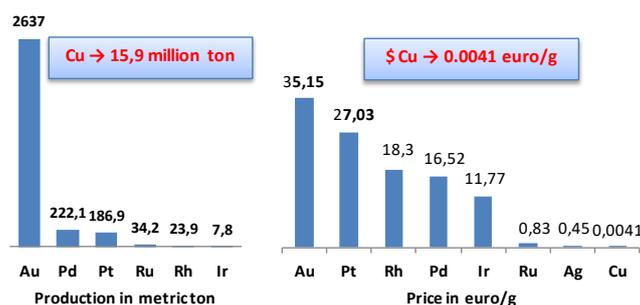
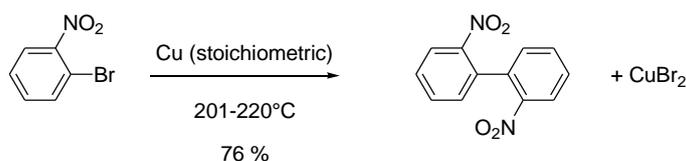


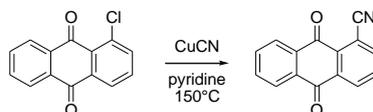
Figure 1. Production of several precious metal in 2010^[5] and prices of several precious metals on March, 22, 2016.^[6]

Historically, copper was often used at the beginning of twentieth-century, but abandoned in fifties in favor of palladium which is used in well-known cross-coupling reactions such as Sonogashira, Suzuki, Heck, and Negishi coupling. In the beginning of 21st century, an interest in copper was reestablished. In 1901, Fritz Ullmann, a German chemist, employed for the first time metallic copper for coupling together two molecules of aryl halides in harsh conditions (scheme 1).^[7] Between 1901 and 1906, Fritz Ullmann and Irma Goldberg extended this reaction to C-O and C-N coupling in the presence of stoichiometric, then catalytic, copper.



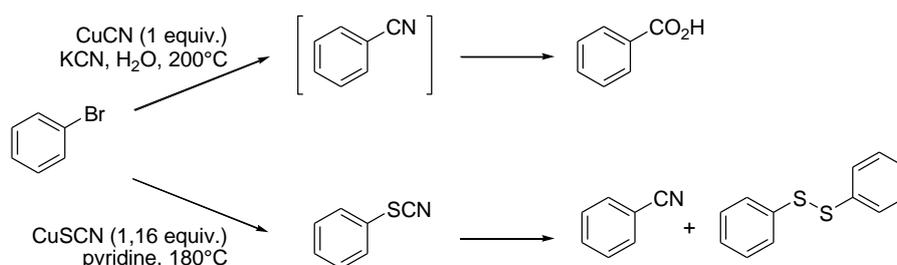
Scheme 1. The Ullmann reaction (1901).

The next major development was the copper-mediated cyanation of aryl halides known as the “Rosenmund—von Braun” reaction. This reaction was firstly described by the Meister, Lucius & Brüning Company in 1913. In pyridine at 150°C, halide-anthraquinones and copper (I) cyanide led to the corresponding nitriles (scheme 2).



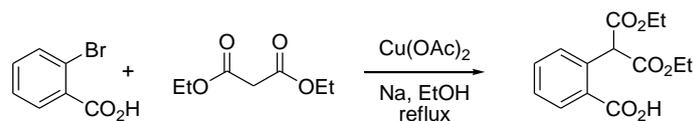
Scheme 2. Copper (I)-mediated cyanation of chloroanthraquinone by the Meister, Lucius & Brüning Company.

A few years after, Karl W. Rosenmund and Erich Struck reported the preparation of benzoic acid from bromobenzene in the presence of potassium cyanide in combination with copper (I) cyanide in water at 200°C (scheme 3).^[8] Then, copper (I) thiocyanate in pyridine was used with aryl bromides to prepare aryl thiocyanates which spontaneously gave the corresponding nitriles at 180°C (scheme 3).^[9] At the same time, many chemists and industrialists developed this reaction.^[10]



Scheme 3. Copper (I)-mediated cyanation of bromobenzene by Rosenmund (1919).

William R. H. Hurtley, inspired by these topics, reported in 1929 the C-arylation of some families of CH-acids in reaction with *o*-bromobenzoic acid in the presence of sodium ethoxide as a base (scheme 4).^[11]

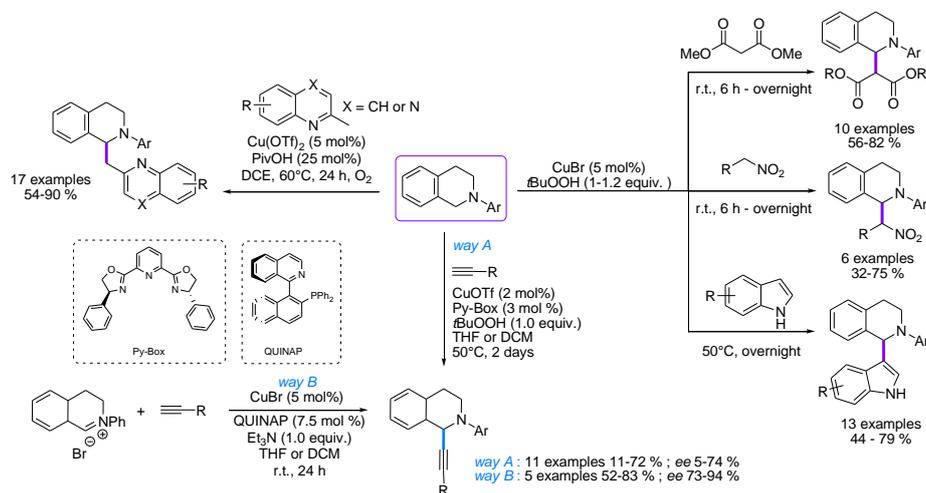


Scheme 4. Copper (II)-mediated arylation of CH-acid derivatives by Hurtley (1929).

Copper as a coupling agent was gradually abandoned with the discovery of palladium catalysed cross-coupling reaction. Sonogashira, Suzuki, Stille, Negishi, Hiyama, and Heck coupling were well-developed. Copper was only used as a co-catalyst in the Sonogashira and Stille reactions. Palladium remained a preferred catalyst until the end of the century. The non-toxicity, ease of handling and low cost of copper catalysts make them attractive for the elaboration of new synthesis methodologies. We intend this microreview to be an overview of the recent methods for the copper-mediated formation of carbon-carbon bonds. These new methodologies will be illustrated by different applications of dehydrogenative cross-coupling, decarboxylative cross-coupling, Sonogashira-type reaction, cross-coupling reactions with organometallic reagents, domino reactions, and finally more atypical reactions.

2. Cross-dehydrogenative coupling (CDC)

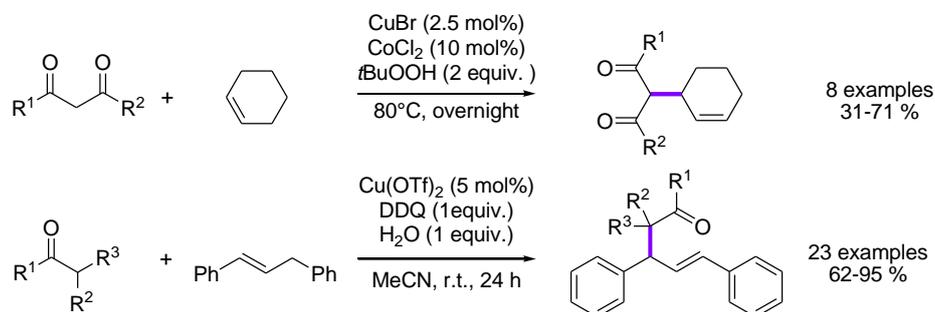
From the perspective of environmentally respectful chemistry, atom economy and direct functionalization of C-H bonds are an essential issue. Cu-catalysed cross-dehydrogenative coupling (CDC) methodologies were developed based on the oxidative activation of C(sp³)-H bonds adjacent to a nitrogen atom. Li and co. reported the first copper-catalysed CDC reaction between C1(sp³)-H bond of tetrahydroisoquinolines and C(sp³)-H of nitroalkane or malonate in the presence of copper bromide as catalyst and *tert*-butylhydroperoxide as oxidant (scheme 5).^[12] This reaction has recently been the subject of mechanistic studies.^[13] Thus, they open the way to many research works about the preparation of C-1-substituted tetrahydroisoquinolines *via* CDC methodologies.^[14] Then they have described the formation of C(sp³)-C(sp²) bonds for direct indolation of tetrahydroisoquinolines^[15] and C(sp³)-C(sp) bonds for asymmetric alkylation of tetrahydroisoquinoline derivatives^[16] (scheme 5). This work focuses on the reactivity of the C(sp³)-H bond of tetrahydroisoquinoline (way A) and of the C(sp²)-H bond of the iminium form (way B). Two ways were highlighted using a combination of chiral ligand, (Py-Box or QUINAP) and copper salt. Both protocols proved effective as enantioselective catalysts. More recently, they reported the asymmetric CDC of alkynes and tetrahydroisoquinolines in the presence of chiral copper catalyst, iridium complex as photocatalyst, and benzoyl peroxide as oxidant. This medium leads to 1-alkynyl tetrahydroisoquinolines in good yields and excellent enantioselectivities.^[17] Yang and co. presented the functionalization of C-1-nonsubstituted tetrahydroisoquinolines with alkylazarenes. The oxidative-cross-coupling was promoted by the copper/Brønsted acid dual catalyst system and the dioxygen as the terminal oxidant under mild reaction conditions (scheme 5).^[18] Su and co. reported solvent-free CDC reactions under high-speed ball-milling conditions for the synthesis of functionalized tetrahydroisoquinolines.^[19] Copper balls have also been combined with chiral ligand for the preparation of optically active tetrahydroisoquinoline derivatives.^[20]



Scheme 5. Preparation of C-1-substituted tetrahydroisoquinolines *via* a copper-catalysed cross-dehydrogenative-coupling reaction.

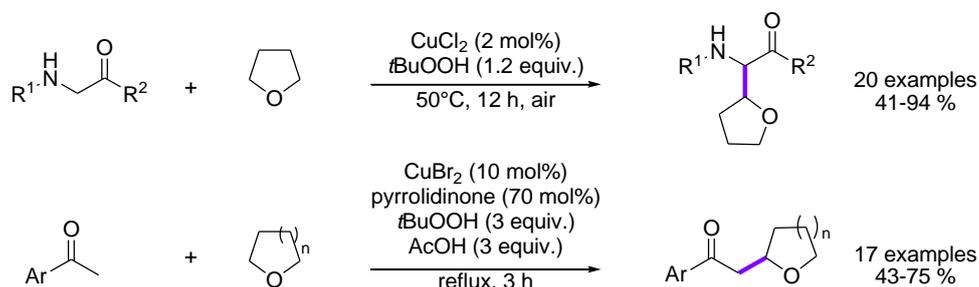
The copper-catalysts have been also employed for the functionalization of the C(sp³)-H bond adjacent to carbonyl group (malonate, ketone, aldehyde, ester) giving large structural variety. Li and co. have developed a catalytic allylic alkylation *via* a Cu/Co-catalysed reaction between allylic C(sp³)-H and methylenic C(sp³)-H bonds (scheme 6).^[21] Another example of copper-catalysed allylic alkylation *via* CDC was illustrated more recently by Huang *et al.* (scheme 6).^[22] They developed a cross-coupling

reaction of common ketones or aldehydes with 1,3-diphenylpropene by using copper trifluoromethanesulfonate as a catalyst and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as an oxidant. They proposed a mechanism using copper triflate as a Lewis acid catalyst to activate ketone or aldehyde.



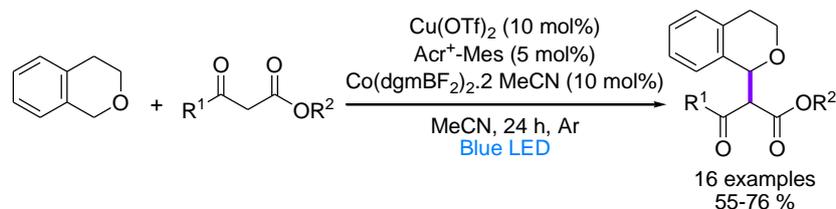
Scheme 6. Allylic alkylation via CDC reaction

Copper-catalysed CDC reactions between unactivated ethers and simple ketones or β -amino carbonyl compounds were also described (scheme 7).^[23] In each case, the coupling reaction was catalysed by copper (II) in the presence of *tert*-butyl hydroperoxide as oxidant, and a radical mechanism was proposed. Various ethers have also been used for the oxidative coupling with nitrones.^[24] Selective C-C bond formation proceeds through cleavage of two C-H bonds concomitant with C=N double bond-migration.



Scheme 7. Copper-catalysed CDC reactions between unactivated ethers and simple ketones or β -amino carbonyl compounds.

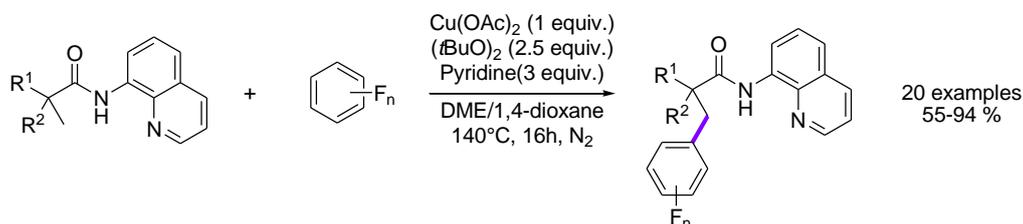
A copper-photocatalytic C-H bond oxidation has been reported for the addition of β -keto ester to isochroman (scheme 8).^[25] This reaction is oxidant-free, and it proceeds via a redox neutral pathway under blue LED.



Scheme 8. Copper-photocatalytic C-H bond oxidation under blue LED.

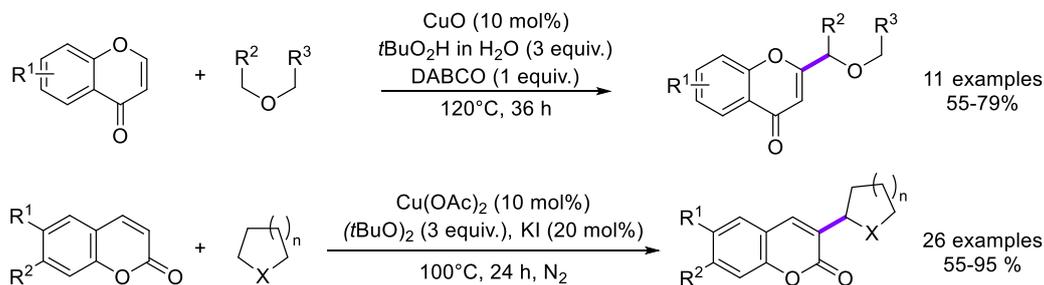
Ge and co. reported an example of arylation of β -carbonyl C(sp³)-H via a copper-promoted CDC reaction (scheme 9).^[26] The coupling reaction occurs from 2-ethyl-2-methyl-*N*-(quinolin-8-

yl)pentanamide and fluoroarenes in the presence of a stoichiometric amount of copper (II) acetate, pyridine and di-*tert*-butylperoxide at 140 °C. The proposed mechanism suggests a different oxidation state of copper (I, II, III).



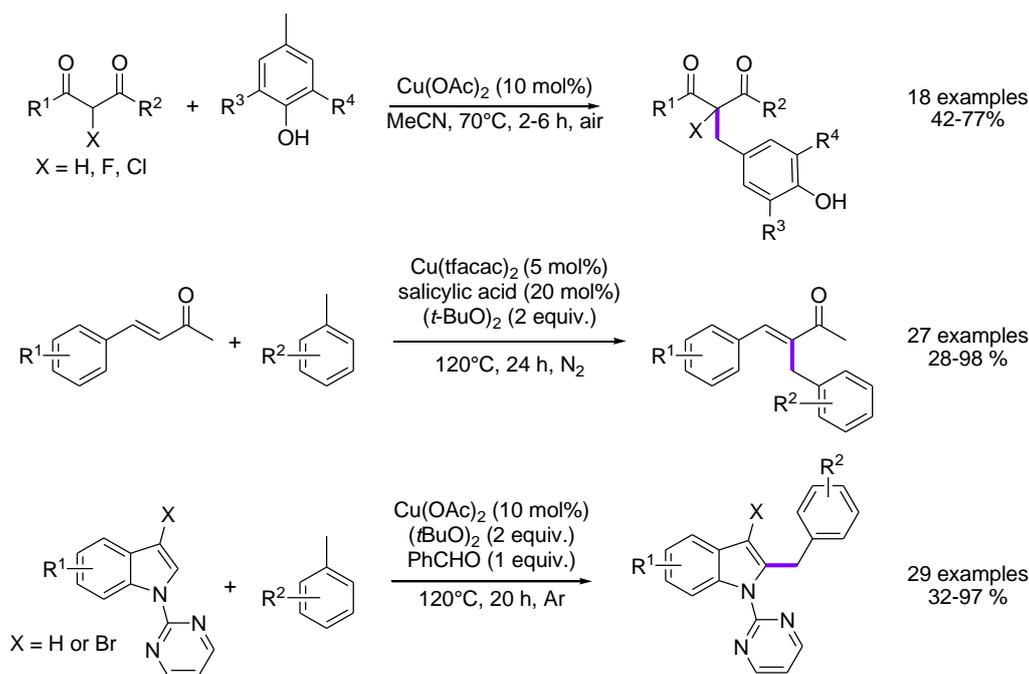
Scheme 9. Arylation of β -carbonyl $C(sp^3)$ -H *via* copper-promoted CDC reaction.

Ge and co. have developed cross-dehydrogenation couplings of ethers with 4*H*-chromen-4-one via $C(sp^3)$ -H functionalization (scheme 10).^[27] The reaction was catalysed by copper oxide in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) as ligand and *tert*-butylhydroperoxide. A radical addition mechanism was proposed. The synthesis of C3-substituted coumarins was reported by Wu and co.^[28] It proceeds *via* copper-catalysed CDC reaction in the presence of di-*tert*-butylperoxide and potassium iodide (scheme 10). The authors proposed a radical mechanism: the *tert*-butylperoxy radical is formed from the redox reaction of (*t*-BuO)₂ with KI and the I₂ formed at the time oxidizes copper acetate in copper (III).



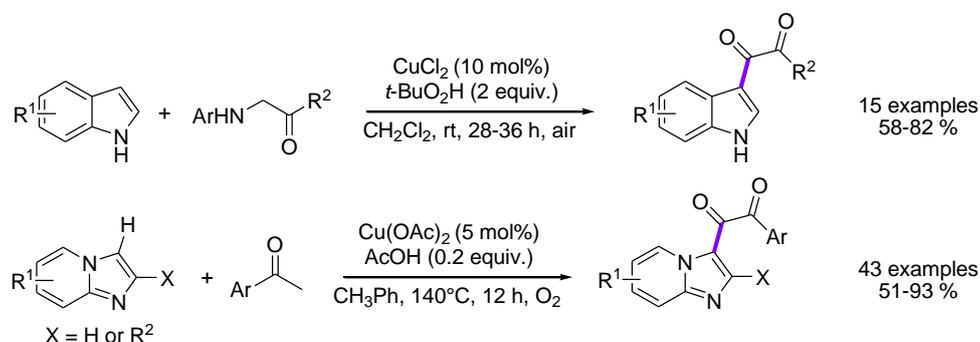
Scheme 10. Cross-dehydrogenation couplings of ethers with 4*H*-chromen-4-ones or coumarines.

Copper-catalysed CDC reactions permit the functionalization of the benzylic $C(sp^3)$ -H bond. The coupling reaction between electron-rich hindered *p*-cresols with fluorinated β -ketone esters and malonates has been developed in the presence of copper acetate as catalyst and oxygen as oxidant (scheme 11).^[29] The mechanism-based reaction formally constitutes a unique double $C(sp^3)$ -H coupling through Michael-type 1,6-addition. Huang and co. investigated α -benzylation of enones *via* radical oxidative cross-coupling.^[30] The reaction is catalysed by copper trifluoroacetylacetonate in the presence of salicylic acid as ligand and di-*tert*-butylperoxide as oxidant (scheme 11). Another example of functionalizations of benzylic $C(sp^3)$ -H has been developed by Wen and co. The CDC reaction between *N*-pyrimidylindones and alkylarenes occurs in the presence of copper acetate as catalyst, di-*tert*-butylperoxide as oxidant and benzaldehyde as an additive (scheme 11).^[31] The use of benzaldehyde as an additive permit to increase the yields, but its real effect remains unclear.



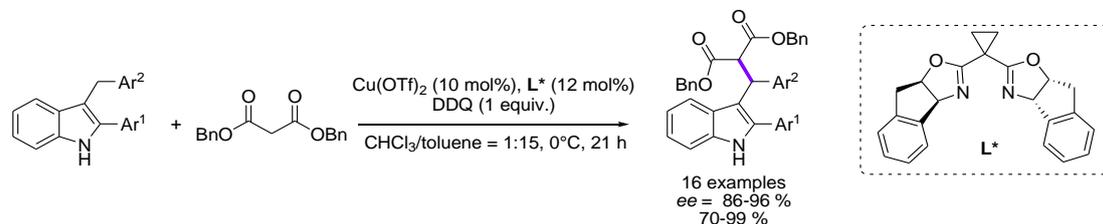
Scheme 11. Functionalization of benzylic C(sp³)-H bond.

Functionalization of various heterocycles has been realized through CDC reactions.^[32] Copper-catalysed CDC reactions with oxidation of C-H bonds have been reported. Miura and co. developed copper mediated direct coupling of 2-arylazines with azoles.^[33] The palladium-free reaction proceeds with a stoichiometric amount of copper acetate. In order to introduce α -amino carbonyl units in natural products or biomolecules, Li and co. investigated coupling between α -amino carbonyl compounds and indole derivatives. In the presence of copper (II), *tert*-butyl hydroperoxide in dichloromethane under air atmosphere, the oxidative coupling products were obtained in good yields (scheme 12).^[34] Recently, Cao and co. described regioselective copper-catalysed oxidative cross coupling of imidazo[1,2-*a*]pyridines with methyl ketones.^[35] The reaction proceeds in the presence of copper acetate as catalyst, acetic acid as additive, and oxygen as terminal oxidant in toluene at 140 °C to lead to desired compounds (scheme 12). Other examples of copper-catalysed dicarbonylation of indole^[36] or imidazo[1,2-*a*]pyridine^[37] derivatives have been recently reported. The reaction proceeds either through a coupling with aryl α -carbonyl aldehydes or *via* an oxidative cross coupling with aryl acetaldehydes.



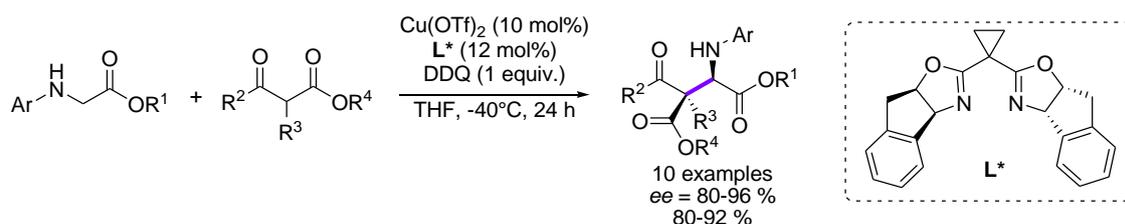
Scheme 12. Copper-catalysed oxidative CDC.

In 2010, Gong and co. described stereoselective CDC reactions for the synthesis of chiral indole derivatives from 3-arylmethylindoles with dibenzylmalonate in the presence of copper (II), chiral bisoxazoline ligand (L^*), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in chloroform/toluene mixture at 0 °C (scheme 13).^[38] The coupling products were obtained with good yields and high enantiomeric excess.



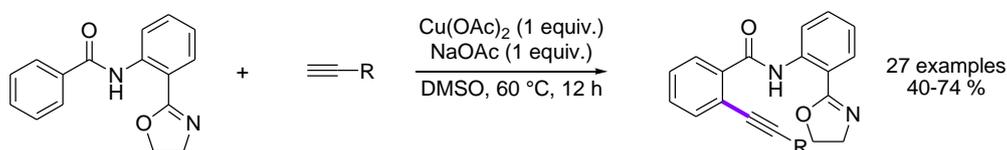
Scheme 13. Enantioselective CDC reaction of 3-arylmethylindole derivatives.

The same catalytic system was used by Wang and co. to prepare optically active α -alkyl- α -amino acids (scheme 14).^[39] The coupling reaction was catalysed by copper (II) in the presence of chiral bisoxazoline ligand (L^*) and 2,3-dichloro-5,6-dicyanoquinone (DDQ) as oxidant, and carried out at -40 °C. The products were obtained in excellent enantioselectivity. Another example of asymmetric CDC reaction has been reported by Habaue and co. in 2006 for the preparation of binaphthyl or quaternaphthyl derivatives.^[40]



Scheme 14. Synthesis of optically active α -alkyl- α -amino acids.

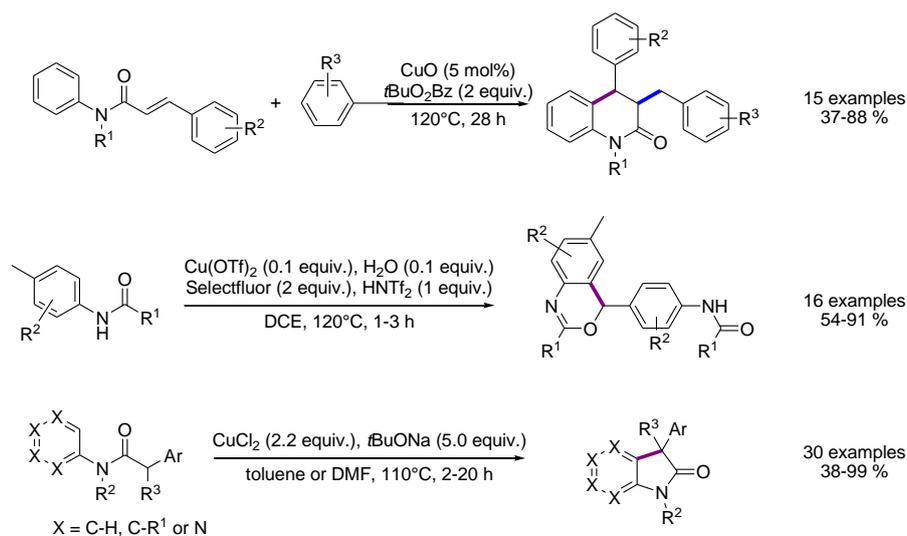
In 2014, Yu and co. reported ortho C-H alkylation of aromatic amides with terminal alkynes.^[41] The coupling reaction was promoted by a stoichiometric amount of copper (II) in the presence of sodium acetate in dimethylsulfoxide at 60 °C (scheme 15). Under the same conditions, alkylation of heteroaromatic amides led to coupling products with modest to good yields.



Scheme 15. Ortho C-H Alkylation of aromatic amides with terminal alkynes.

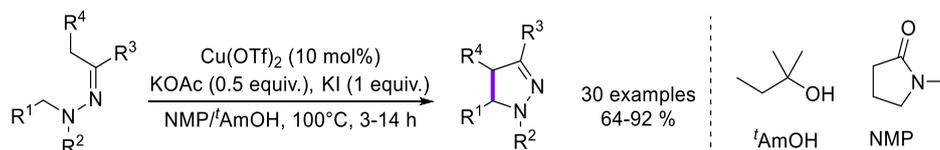
Several copper-catalysed coupling reactions have been followed by a cyclization reaction to constitute various heterocycles. A new C(sp³)-C(sp²) bond was formed during the process. Duan and co. have developed a tandem intermolecular radical addition and an intramolecular 6-*endo*-trig cyclization reaction that provides direct access to functionalized dihydroquinolinones (scheme 16).^[42] During the process, two new bonds were formed: C(sp³)-C(sp³) and C(sp³)-C(sp²) bonds. The reaction was catalysed by copper (I) oxide in the presence of *tert*-butylperoxybenzoate and a radical mechanism

was proposed. $\text{Cu}(\text{OTf})_2$ -catalysed coupling reaction was used for the construction of benzoxazine derivatives from two molecules of *N*-paratolyamides in the presence of Selectfluor and water (scheme 16) [43] The CDC reaction from aromatic $\text{C}(\text{sp}^2)\text{-H}$ and benzylic methyl $\text{C}(\text{sp}^3)\text{-H}$ bonds led to the formation of the C-C bond and the intramolecular C-O bond. In 2009 and 2012, Künding and co. reported the synthesis of 3,3-disubstituted oxindoles and 3,3-disubstituted azapyridyl in modest to excellent yields (scheme 16). [44] The reaction was catalysed by copper (II) in the presence of sodium butanolate in *N,N*-dimethylformamide or toluene. It proceeds *via* a direct intramolecular oxidative coupling of $\text{C}(\text{sp}^3)\text{-H}$ and $\text{C}(\text{sp}^2)\text{-H}$ bond.



Scheme 16. CDC reaction followed by cyclization reaction.

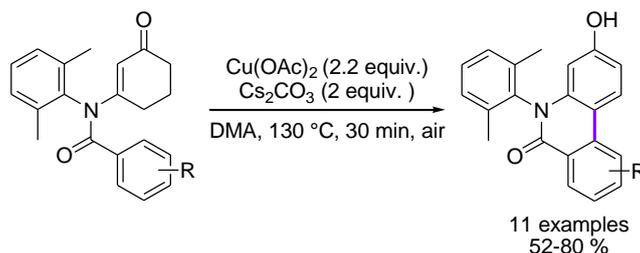
A diastereoselective aerobic intramolecular dehydrogenative cyclization of *N,N*-disubstituted hydrazones was developed using a copper-catalysed CDC coupling reaction (scheme 17). [45] A 5-center/6-electron disrotatory cyclization mechanism was proposed to rationalize the observed diastereoselectivity. This original copper-catalysed C-C coupling with good functional group tolerance provides a straightforward, environmentally friendly, and atom-efficient access to pyrazolines with up to five fused-ring systems. Recently, Mao et al. reported copper-promoted $\text{C}(\text{sp}^3)\text{-C}(\text{sp}^3)$ bond homocoupling to form tetrasubstituted furans in the presence of trifluoroacetic acid and a catalytic amount of $\text{Cu}(\text{OAc})\cdot\text{H}_2\text{O}/\text{AgNO}_3$ in xylene. [46] Various substitutes such as methyl, methoxy, fluoro, chloro, bromo, and nitro group were tolerated under reaction conditions.



Scheme 17. Original copper-catalysed C-C coupling to synthesize pyrazolines.

Zhao and co. investigated the intramolecular CDC reaction from *N*-(3-oxocyclohex-1-enyl)benzamides. [47] The reaction starts *via* a cascade C-C coupling followed by dehydrogenative aromatization in the presence of copper(II) acetate and cesium carbonate in *N,N*-dimethylacetamide (DMA), at 130 °C

under air atmosphere. Desired 3-hydroxyphenanthridine-6(5*H*)-ones were obtained with moderated to good yields (scheme 18).

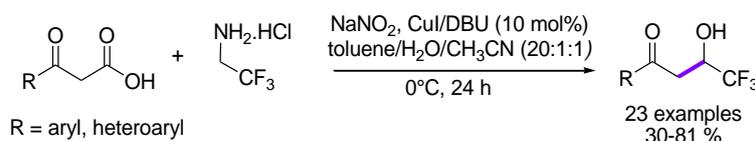


Scheme 18. Cu-mediated CDC cyclization followed by aromatization.

3. Decarboxylative coupling reactions

In usual conditions, cross coupling reactions take place between halogenated compound and organometallic reagent. Decarboxylative coupling (DCC) reactions are of contemporary interest in order to substitute relatively inexpensive carboxylic acids.^[48] Carboxylic acids are air and moisture insensitive, and easy to store and handle. During DCC reaction, they generate only carbon dioxide instead of metallic wastes. Here, few examples of functionalization of C(sp³)-CO₂H, C(sp²)-CO₂H or C(sp)-CO₂H bond *via* DCC reaction will be presented.

A one-pot transformation involving denitrogenative-deshydrogenative-decarboxylative coupling of β -ketoacids and trifluorodiazaoethane was reported by Ma and co. (scheme 19).^[49] This coupling is a rare example of C(sp³)-C(sp³) bond formation with introduction of trifluoromethane motif. The optimal conditions are generated *in situ* 2,2,2-trifluorodiazaoethane (CF₃CHN₂) with γ -aryl-substituted β -ketoacids in the presence of CuI in DMF. During this reaction, one C-C bond and one C-O bond are constructed in a carbenoid center thanks to three cascade reactions: denitrogenation, deshydrogenation, and decarboxylation. The isotopic labelling experiments were performed to gain preliminary understanding of the mechanism in D₂O and in ¹⁸O₂. They showed that water can transfer an oxygen atom into the cross-coupling product under copper catalysis.

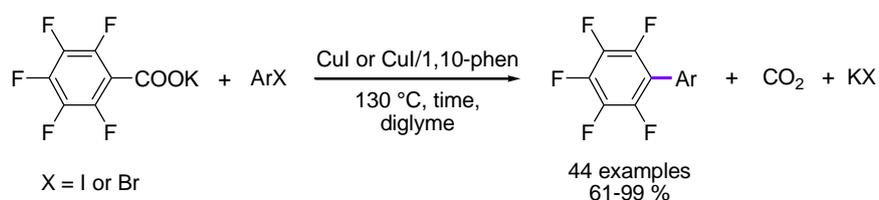


Scheme 19. Denitrogenative-deshydrogenative-decarboxylative coupling of β -ketoacids and trifluorodiazaoethane.

Benzoic acid derivatives were used for arenes arylation in order to obtain polyfluorobiaryls, which are important molecules in medicinal chemistry^[50] and in material science.^[51] Liu and co. described for the first time copper-only systems that catalyze the decarboxylative cross-coupling of potassium polyfluorobenzoates with aryl iodides and bromides.^[52]

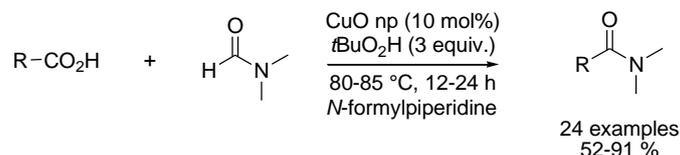
The reaction can replace the use of expensive but less reactive fluorobenzene organometallics in the synthesis of polyfluorobiaryls. It occurred at 130 °C with diglyme as solvent, which facilitated the complexation between CuI and the carboxylate. The catalyst depended on the aryl used. Actually, using

aryl iodides permitted to use the copper iodide as a catalyst only. When aryl bromide are employed, 1,10-phenanthroline must be added as a ligand in order to get similar results as the aryl iodides (scheme 20). The reaction yields range from good to excellent. In addition, different aryl substrates including naphthyl and heteroaryl can also be used to form the corresponding polyfluorobiaryls. Based on theoretical analyses, decarboxylation took place at first on copper(I) to generate a polyfluorophenylcopper(I) intermediate. Then, it reacted with aryl halides through oxydative addition and reductive elimination to produce the coupling products.



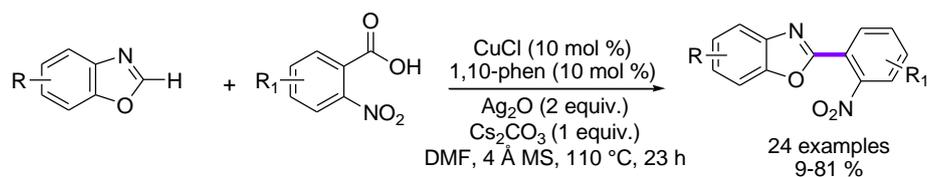
Scheme 20. Copper-catalysed the decarboxylative cross-coupling of potassium polyfluorobenzoates with aryl iodides and bromides.

Kantam and co. reported a recyclable catalytic protocol for amidation of arenes. Various carboxylic acids were engaged for oxidative coupling with *N,N*-dimethylformamide catalysed by CuO nanoparticles in the presence of *tert*-butyl hydroperoxide in *N*-formylpiperidine (scheme 21).^[53] The protocol affords the corresponding *N,N*-dimethyl- substituted amides in good yields and excellent regioselectivity.

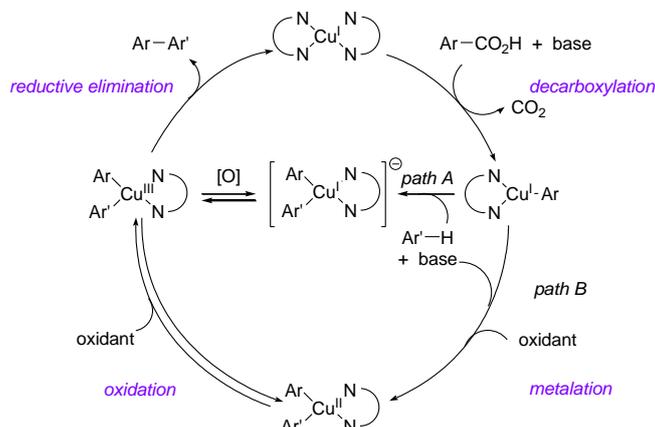


Scheme 21. CuO catalysed oxidative coupling for obtaining *N,N*-dimethyl substituted amides.

Recently, an example of heterocyclic arylation between benzoxazole and 2-nitrobenzoic acid was reported by Hoover and co. (scheme 22).^[54] After studying the scope of both reagents, decarboxylative arylation conditions could be done to a wide range of electron-deficient 2-nitrobenzoic acids and electron-rich benzoxazoles. The heterobiaryl products were obtained for the majority in good yields. Heteroarenes with two heteroatoms (O, N, or S) were also developed by Maiti and co.^[55] They demonstrated that in their conditions (CuBr/1,10-phen/ $\text{K}_2\text{CO}_3/\text{O}_2$ in toluene), the thiophene pattern can be employed, while they are less reactive thanazole derivatives. The authors proposed a plausible mechanism for their protocol (scheme 23). The ligated copper forms aryl-copper intermediate *via* decarboxylation. Then two pathway were envisaged: metalation of arene $\text{Ar}'\text{H}$ with aryl-copper species may lead to either the Cu(I) intermediate (pathway A) or the Cu(II) intermediate (pathway B) by instantaneous oxidation. A reversible oxidation from these two possible intermediates lead to the Cu(III) complex followed by a reductive elimination to furnish coupling product and ligated copper.

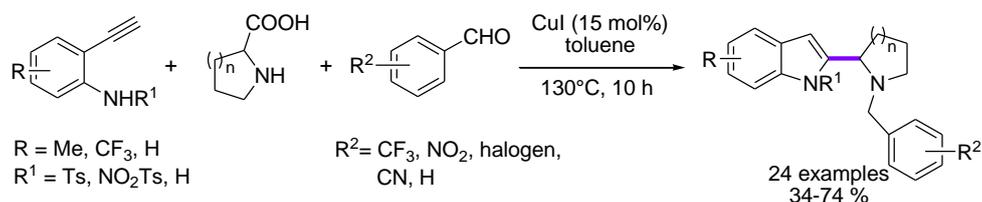


Scheme 22. Copper-catalysed decarboxylative C-H arylation.



Scheme 23. Plausible mechanism of Copper-catalysed decarboxylative C-H arylation.

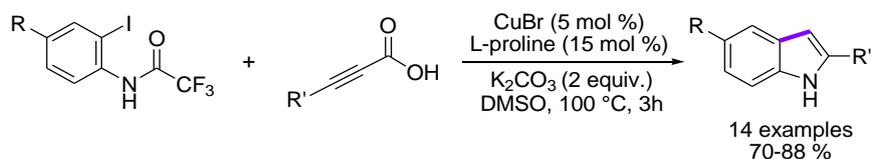
In 2009, Li and co. investigated the copper-catalysed decarboxylative coupling of α -amino acids with terminal alkynes.^[56] In 2015, Wu and co. reported the functionalization of indoles *via* DCC reaction cyclic α -amino acids during a domino three-component reaction (scheme 24).^[57] The indoles were prepared *in situ* by *N*-tosylated 2-ethynylaniline cyclization. In this way, 2-(2-indolyl)pyrrolidine products were prepared with moderate to good yields in the presence of catalytic amount of copper iodide at 130 °C under argon. Another example of the domino three-component reaction with decarboxylative coupling as a key step has been reported the same year by Sun and co.^[58] 1,4-diheterocycle-2-butynes were prepared in one step from propiolic acid, formaldehyde and β -aminoalcohol under microwaves radiations with good yields.



Scheme 24. Domino three-component decarboxylative coupling reaction.

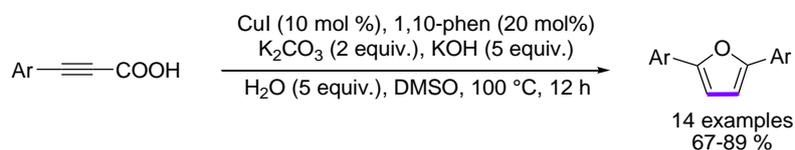
DCC is well-employed for the synthesis of natural product cores, such as indoles and furans. Five membered heterocycles are recognized as important structural motifs in pharmaceuticals, agrochemicals, natural products, functional organic materials and dye industries.^[59] The coupling reaction is often followed by cyclization in order to form heterocycles. An example of this strategy was reported by Muthusubramanian and co.^[60] Decarboxylative cross coupling and cyclization of alkynyl carboxylic acids with substituted 2-iodotrifluoroacetanilide were achieved with copper (I)/L-proline

catalytic system (scheme 25). The reaction tolerated a wide range of functional groups, which can be useful for the synthesis of 2-aryl substituted indoles in good yields.



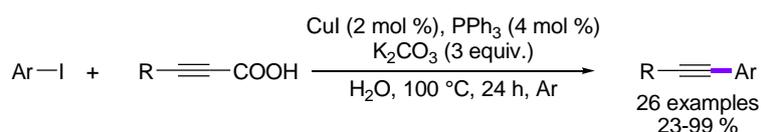
Scheme 25. Synthesis of 2-aryl substituted indoles.

Domino one-pot synthesis of 2,5-diarylsubstituted furans *via* decarboxylative homocoupling reaction followed by cyclization of aryl alkynyl carboxylic acids was published by Lee and co. (scheme 26).^[61] No by-product was obtained except CO₂ and the reactions occurred with high conversion and selectivity of the desired product. A broad substrate scope was screened giving the 2,5-diarylsubstituted furans with good to excellent yields.



Scheme 26. Copper-catalysed one-pot synthesis of 2,5-diarylsubstituted furans.

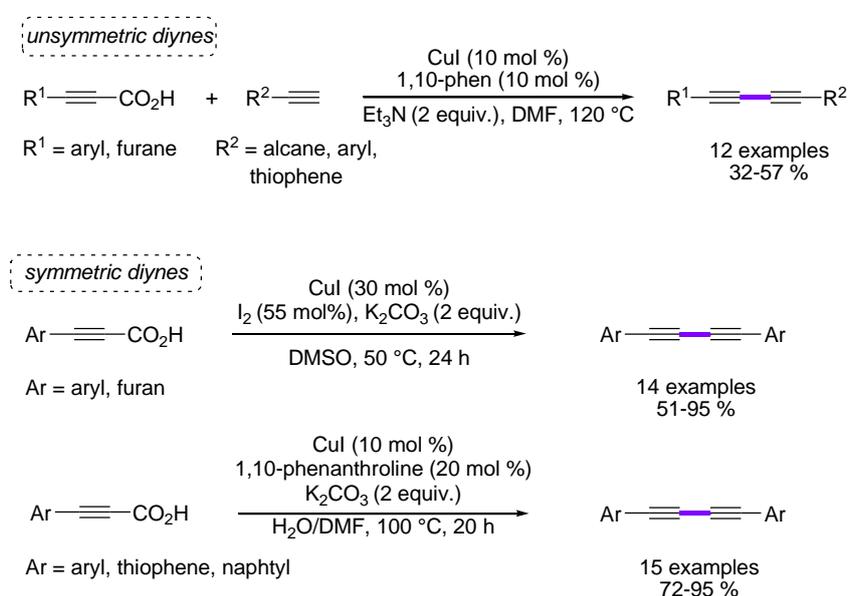
In 2012, Mao and co. reported an example of a palladium-free Sonogashira DCC reaction between aryl iodides and alkynyl carboxylic acids (scheme 27).^[62] The reaction performed in the presence of copper iodide as catalyst, triphenylphosphine as ligand, and potassium carbonate as base in water at 100 °C. The desired products were isolated with good yields. In the same year, Mao and co. described copper catalysed DCC reaction between acid cinnamic derivatives and benzylic compounds.^[63] The reaction proceeds with good stereoselectivity *via* a radical mechanism.



Scheme 27. Sonogashira decarboxylative cross-coupling.

Decarboxylative homocoupling reactions permit access to diynes patterns. Diynes are important structural motifs in natural products as well as building blocks in organic synthesis. Oxidative homocoupling reaction of terminal alkynes was first reported by Glaser.^[64] This coupling is well-applied in the construction of symmetric diynes. For over six decades, Cadiot-Chodkiewicz coupling using a Cu-catalyst has been the main method for constructing unsymmetric conjugated diynes.^[65] However, halogenated substrates or alkynyl metal reagents were required and halide by-products were produced in these methods. Nowadays, chemist communities look for alternatives to formation of toxic by-products and favor the use of green-transition metals. Different examples are here reported for the synthesis of unsymmetric and symmetric diynes. Jiao and co. have described copper-catalysed decarboxylation cross-coupling between alkynyl carboxylic acids and terminal alkynes. C(sp)-C(sp)

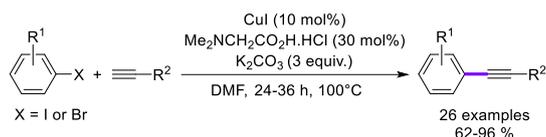
bonds have been formed to lead to unsymmetric diynes with moderate yields (scheme 28).^[66] Another methodology to synthesis unsymmetric diynes have been developed by Fu and co. from 1,1-dibromo-1-alkenes and potassium alkynyl carboxylates.^[67] In this way, decarboxylative cross-coupling reactions proceed with high selectivity. From the literature, studies of synthesis of symmetric diynes were also reported. Recently, Lang and co. published two catalytic systems for copper-catalysed oxidative decarboxylative homocoupling of aryl propiolic acids.^[68] Actually, aryl propiolic acids in the presence of copper iodide as catalyst and iodide as oxidant permit the synthesis of 1,4-diarylsubstituted 1,3-diynes in good yields. At the same time they published more environmentally advantageous conditions. The reaction takes place in the presence of copper iodide and 1,10-phenanthroline as a catalytic system and potassium carbonate as base in mixture solvent (DMF/H₂O). Diynes products are insoluble in the aqueous-DMF phase and can be easily removed by simple filtration. Consequently, the aqueous-DMF solution can be easily recycled. By this protocol, 1,4-diarylsubstituted 1,3-diynes in good yields.



Scheme 28. Synthesis of unsymmetric and symmetric diynes.

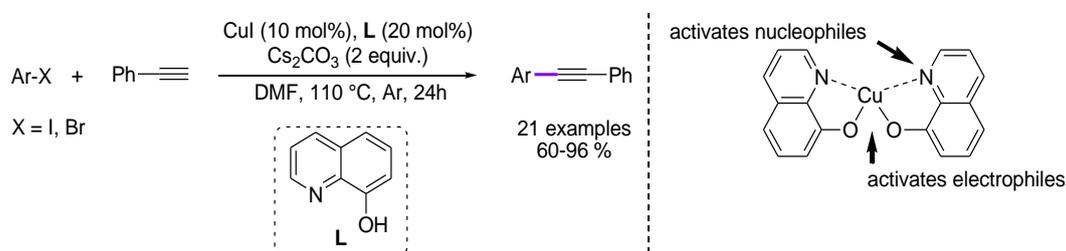
4. Palladium free Sonogashira cross-coupling reaction

Uncovered in 1975,^[69] the Sonogashira reaction is a powerful synthetic method for the construction of C(sp²)-C(sp) bonds by the introduction of a triple bond into aromatic systems *via* cross-coupling of aryl halides and terminal alkynes.^[70] This reaction generally employs Pd(PPh₃)₂Cl₂ or Pd(PPh₃)₄ and copper(I) iodide as the catalytic system. Because of palladium cost, many efforts have been directed to explore new catalytic systems as the employment of nickel instead of palladium.^[71] Recent attention has been focused on employing copper-only catalytic systems in Sonogashira coupling reactions. First examples were described in 2004. Ma and co. reported coupling reaction of aryl halides with terminal alkynes in the absence of palladium and phosphine (scheme 29).^[72] Copper iodide/*N,N*-dimethylglycine hydrochloride salt was used as a catalytic system. Without ligand, the reaction gave only traces of desired compound. The same year, Rothenberg and co. reported palladium-free and ligand-free Sonogashira cross-coupling reaction with copper nanocluster as catalyst.^[73]



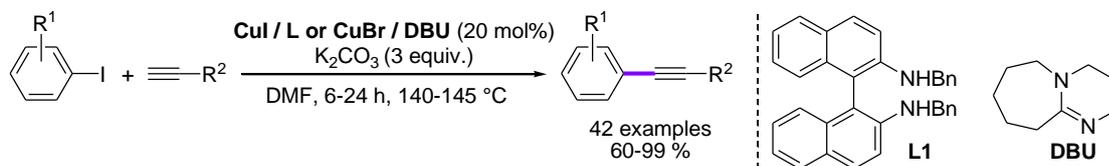
Scheme 29. CuI/*N,N*-dimethylglycine catalysed coupling reaction of aryl halides with terminal alkynes.

This new approach of Sonogashira coupling reaction allowed the development of copper catalytic systems^[74] such as copper nanoparticles,^[75] supported copper catalyst,^[76] or the use of various ligands.^[77] For example, Mao and co. reported copper catalyst cross-coupling reactions of aryl halides with terminal alkynes in the presence of cesium carbonate in *N,N*-dimethylformamide at 110 °C (scheme 30).^[78] The products were obtained with good yields, except from arylchloride in which lower yields were observed. The reaction is based on a bifunctional catalyst system generated *in situ* where two different parts could lead to double activation.



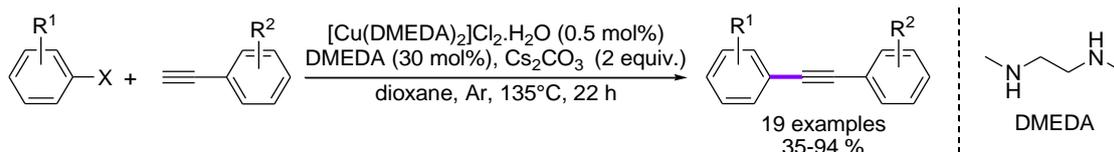
Scheme 30. Cross-coupling of aryl halides and phenylacetylene catalysed by the possible copper-based bifunctional catalyst system.

In 2009, Sekar and co. developed the synthesis of arylated alkynes from aryl iodides and terminal alkynes through Sonogashira type cross-coupling reaction catalysed by ligand/Cu(I) complex in the presence of potassium carbonate in *N,N*-dimethylformamide at 140 °C (scheme 31).^[79] *N,N*-dibenzyl-1,1'-binaphthyl-2,2'-diamine or 1,8-diazabicyclo[5.4.0]undec-7-ene (respectively **L** and **DBU** in scheme 30) were employed as efficient ligands.



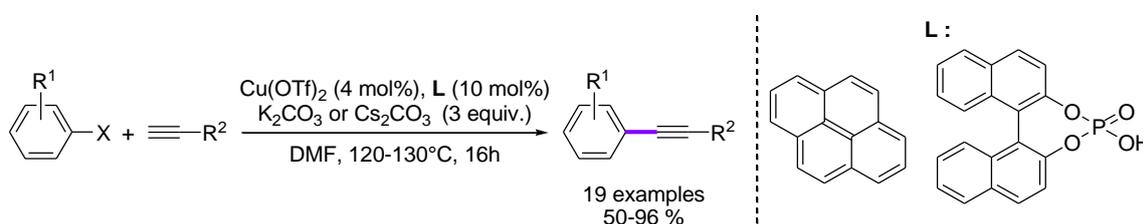
Scheme 31. Cross-coupling of aryl halides with terminal alkynes in the presence of Ligand-Cu(I) catalyst.

Bolm and co. described a new catalytic system with copper (II) in combination with *N,N'*-dimethylethylenediamine (DMEDA) for a coupling between various aryl iodides and terminal aryl alkynes (scheme 32).^[80] Interestingly, only 0.5 mol% of catalyst is required for obtaining desired compounds in good yield.



Scheme 32. Cross-coupling of aryl halides with aryl alkynes in the presence of $[\text{Cu}(\text{DMEDA})_2]\text{Cl}_2\cdot\text{H}_2\text{O}$ and DMEDA.

Recently, Gao and co. described Sonogashira-type cross-coupling reactions accelerated by polycyclic aromatic hydrocarbons^[81] or by organophosphate.^[82] Aryl iodides and aliphatic or aromatic terminal alkynes lead to coupling compounds in the presence of copper triflate, pyrene, or organophosphate as ligand and a base in DMF (scheme 33). Aryl iodides bearing either electron-donating or electron-withdrawing substituents react with arylalkynes in order to afford the desired products with good to excellent yields.



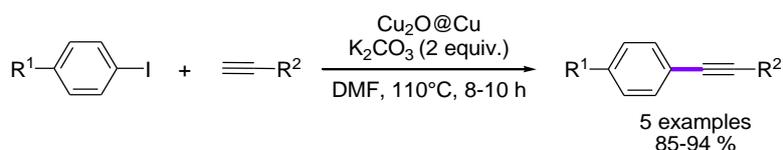
Scheme 33. Cu(I)/L-catalysed Sonogashira cross coupling of aryl iodides and terminal alkynes.

Alternatives to the use of ligand have also been developed. In 2012, Hwang and co. reported that the simple CuCl salt catalysed the Sonogashira reaction with high yields (80-99%) under blue LED light irradiation at room temperature. They first demonstrated a novel photo-initiated CuCl-catalysed Sonogashira cross-coupling reaction between a large variety of aryl iodides and terminal alkynes (scheme 34).^[83] Trace amount of diynes products were obtained.



Scheme 34. Visible light-mediated Sonogashira cross-coupling reaction.

Kou and co. demonstrated the use of inside-out core shell architectures ($\text{Cu}_2\text{O}@\text{Cu}$) with a copper (I) oxide core and a copper (0) shell for the Sonogashira coupling reactions. The $\text{Cu}_2\text{O}@\text{Cu}$ composite exhibits an excellent catalytic activity for the Sonogashira coupling reactions between aryl iodides and phenylacetylenes (scheme 35).^[84]



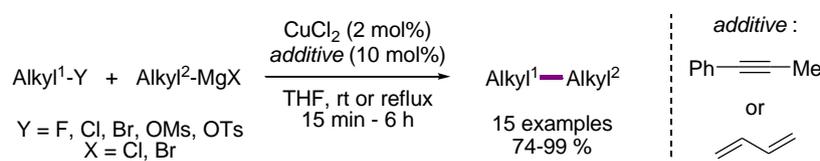
Scheme 35. Sonogashira coupling reactions of aryl iodides with phenylacetylenes.

5. Cross-coupling reaction with organometallic reagents

Palladium is well-known for catalysing cross-coupling reactions between halide compounds and organometallic reagents as Grignard reagents,^[85] aryl- or vinyl boron compounds,^[86] and organozinc reagents.^[87] The cost of palladium catalysts push into using alternative catalysts as nickel^[88] or copper.

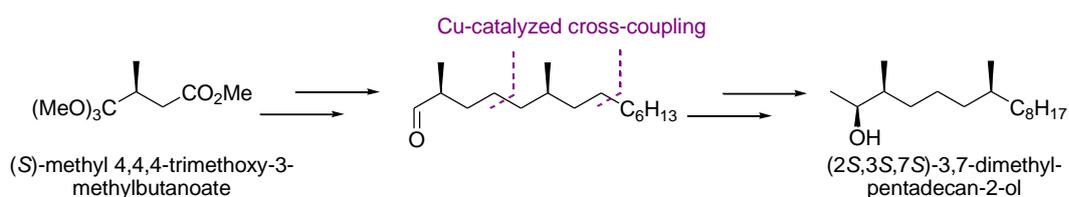
5.1. Grignard reagents

For the construction of alkyl chains, copper catalysed the coupling reaction of Grignard reagents and alkyl halides. In 1972, a seminal work realized by Tamura and co. describes the cross-coupling reaction between various Grignard reagents and primary alkyl bromides with a copper catalyst to produce cross-coupled dimers.^[89] Remarkable progresses were performed by Kambe and co. They showed the effective cross-coupling reaction between alkyl chlorides, fluorides, mesylates, or tosylates, and Grignard reagents in the presence of 1-phenylpropyne as an additive (scheme 36).^[90]



Scheme 36. Cross-coupling reaction between alkyl chlorides, fluorides, mesylates or tosylates, and Grignard reagents.

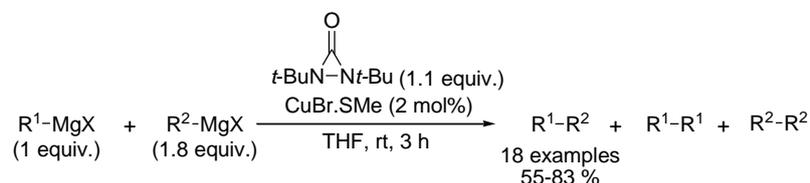
According to this robust methodology, Murata and co. have prepared isotope cluster-labeled long chain fatty acids *via* two consecutive C(sp³)-C(sp³) copper-catalysed cross-coupling reactions.^[91] Copper-catalysed Grignard cross-coupling reaction was also used for the preparation of the carbon skeleton of (2*S*,3*S*,7*S*)-3,7-dimethylpentadecan-2-ol and its propionate, with high enantiomeric purity from (*S*)-methyl 4,4,4-trimethoxy-3-methylbutanoate (scheme 37).^[92]



Scheme 37. Preparation of long carbon skeleton *via* copper-catalysed Grignard cross-coupling reaction.

More recent methodologies for alkyl-alkyl cross-coupling reactions have been developed. For examples, Hu and co. reported the coupling of functionalized alkyl halides and tosylates with secondary and tertiary alkyl Grignard reagents catalysed by copper chloride in tetrahydrofuran at room temperature.^[93] This efficient method tolerates a wide variety of functional groups. Liu and co. investigated the coupling between nonactivated alkyl halides, tosylates and mesylates with Grignard reagents.^[94] The reaction is catalysed by copper iodide in the presence of *N,N,N',N'*-tetramethylethylenediamine and lithium methanolate as additives in tetrahydrofuran. In some cases, the organomagnesium compound is generated *in situ*. This reaction occurs *via* a stereocontrolled S_N2 mechanism with inversion of configuration.

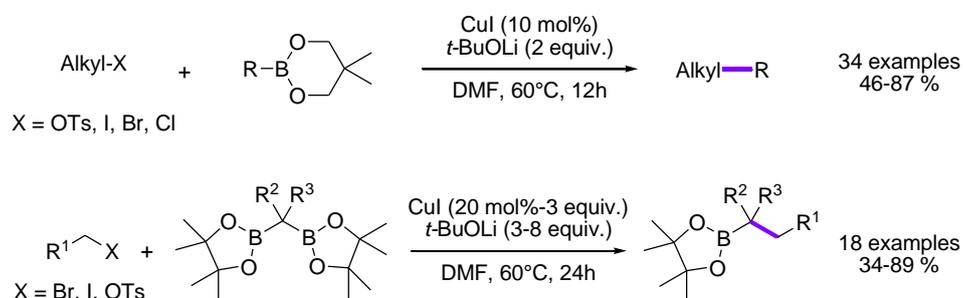
Copper catalyzing the homo- and cross-coupling reaction of Grignard reagents using di-*tert*-butyldiaziridinone as oxidant was reported by Shi and co.^[95] Aryl, alkynyl, and alkyl Grignard reagents can be coupled to give the corresponding homo-coupling products in good yields (73-98 %). The use of two Grignard reagents could lead to the formation of three coupling products. However, the desired cross-coupling product was formed with high selectivity and isolated with good yield (scheme 38).



Scheme 38. Copper-catalysed oxidative cross-coupling of Grignard reagents.

5.2. Boronic reagents

Organoboron compounds are also used to functionalize nonactivated primary halogeno alkyl *via* a copper-promoted Suzuki–Miyaura cross-coupling. Liu and co. developed a cross-coupling of alkyl electrophiles with organoboron compounds catalyzed by copper iodide in the presence of lithium *tert*-butoxide, as crucial base, in *N,N*-dimethylformamide (scheme 39).^[96] According to this methodology, Fu and co. described the preparation of alkylboronic esters from *gem*-diborylalkane (scheme 39).^[97] A catalytic amount of copper iodide is adequate for the reaction of the *gem*-diborylmethane, when a stoichiometric quantity is required for the coupling of substituted 1,1-diborylalkanes. These conditions were exploited for the coupling reaction of allyl boron ester with primary, secondary, and even tertiary halogenated alkanes.^[98]

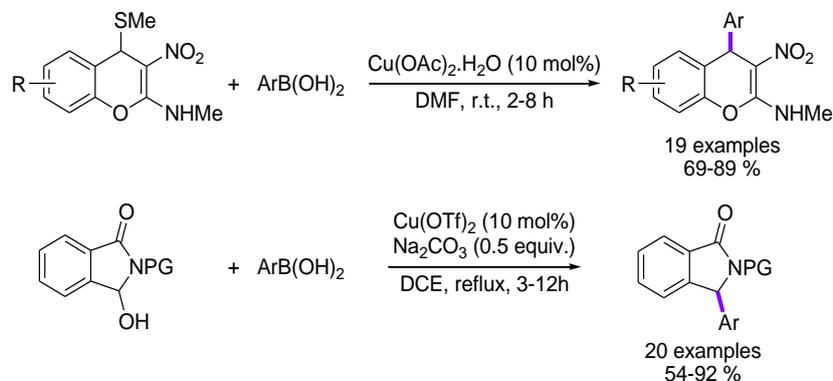


Scheme 39. Coupling reaction of organoboron compounds with halogenated alkanes

Organoboron compounds were very used to synthesise biaryl compounds *via* Suzuki–Miyaura cross-coupling reaction. In 2000, Rothenberg and co. investigated the use of mixed nanocluster catalysts for the coupling of aryl iodides with boronic acids.^[99] Total conversion was observed in two hours with mixed palladium/copper colloids and in eight hours with copper colloids.

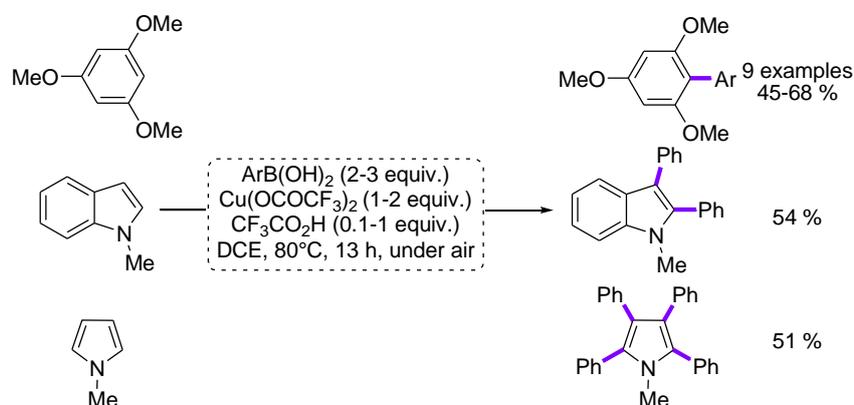
Giri and co. reported the copper-catalysed coupling reaction between aryl- and heteroarylboronate esters and aryl halides, in the presence of 2-(di-*tert*-butylphosphino)-*N,N*-dimethylbenzenamine as ligand, and cesium fluoride as base, for the synthesis of biaryl compounds with modest to good yields.^[100] Arylation of heterocycles using arylboronic acids have been described by Rao and co. In 2014, the arylation of *N*-methyl-4-(methylthio)-3-nitro-4*H*-chromen-2-amines was catalysed by copper (II) in DMF under anaerobic conditions (scheme 40).^[101] This reaction is the first example of a copper-

catalysed coupling reaction with C(sp³)-SMe bond. In 2015, they reported the synthesis of 3-substituted isoindolinones *via* a cross-coupling reaction between 3-hydroxyisoindolinones and aryl-, heteroaryl-, and alkenylboronic acids (scheme 40).^[102] C(sp³)-OH bond cleavage with concomitant C-C coupling were copper-catalysed.



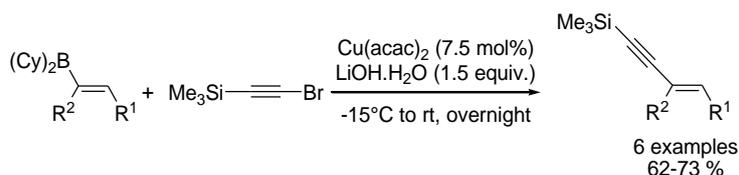
Scheme 40. Synthesis of 3-substituted isoindolinones *via* cross-coupling.

In 2008, Itami and co. reported copper-mediated C-H bond arylation of arenes with arylboronic acids.^[103] Copper trifluoroacetate promoted functionalization of C(sp²)-H bond in the presence of aryl boronic acid, trifluoroacetic acid in 1,2-dichloroethane at 80 °C (scheme 41). This methodology allowed arylation of 1,3,5-trimethoxybenzene, *N*-methylindole and *N*-methylpyrrole with modest yields.



Scheme 41. Copper-mediated C-H bond arylation of arenes with arylboronic acids.

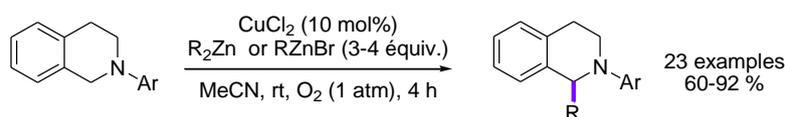
Hoshi and co. described preparation of terminal enynes through cross-coupling reaction between alkenyldialkylborane and (trimethylsilyl)ethynyl bromide.^[104] The reaction proceeds in the presence of copper(II) acetylacetonate and hydroxide lithium as base (scheme 42). The use of sodium methanolate as base leads to desilylated cross-coupling product.



Scheme 42. Synthesis of enyne compounds *via* Cu-catalysed cross-coupling reaction.

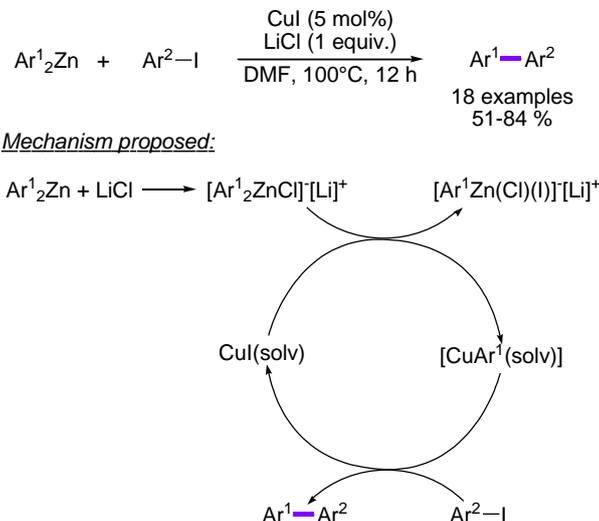
5.3. Organozinc reagents

In 2004, Ready and co. developed cross-coupling reaction of alkylzinc halides with α -chloroketones for the synthesis of α -branched ketones.^[105] The alkylzinc halides was generated through transmetalation of the corresponding Grignard reagent with zinc chloride. In 2015, Menche and co. reported cross-coupling reaction between organozinc reagents and tetrahydroisoquinolines catalysed by copper(II) under aerobic conditions (scheme 43).^[106] The mechanism proposed is based on an iminium ion intermediate formed *via* an organic radical involving a single-electron-transfer process.



Scheme 43. C-1 alkylation of tetrahydroisoquinoline *via* cross-coupling reaction with organozinc reagent

In 2015, Giri and co. reported cross-coupling reaction between alkyl-, aryl-, and alkynylzinc halides and heteroaryl halides.^[107] The reaction proceeds in the presence of catalytic amount of copper iodide, and lithium chloride in *N,N*-dimethylformamide at room temperature. According to this methodology, they investigated the coupling reaction between diarylzinc reagents with aryl iodides (scheme 44).^[108] In this case, the reaction was performed at 100 °C. The mechanism proposed involves a transmetalation between copper(I) iodide and diarylzincate complex generated *in situ* from lithium chloride and diarylzinc reagent. Then, the [CuAr] complex reacts with aryl iodide to afford biaryl products (scheme 44).

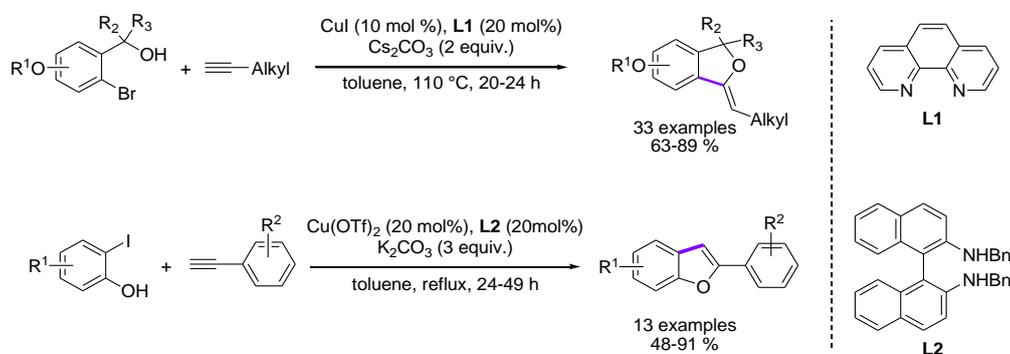


Scheme 44. Coupling of diarylzinc reagents with aryl iodides, mechanism proposed.

5.4. Other organometallic reagents

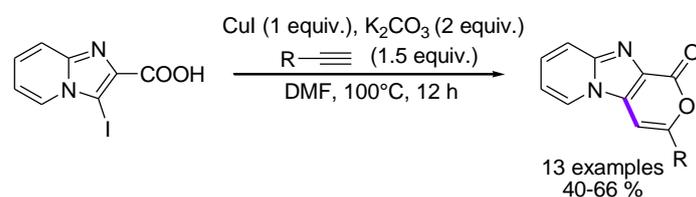
Giri and co. investigated copper iodide associated to 2-(diphenylphosphino)-*N,N*-dimethylbenzenamine (PN) as ligand in cross-coupling reaction. Using this catalytic system, they reported the coupling reaction between alkyl-, aryl- and alkynylaluminium reagents with aryl-, heteroaryl halides, and vinyl bromides (scheme 45).^[109] This catalytic system was also employed in the Hiyama reaction for the coupling of aryl iodides with a aryltriethoxysilanes (scheme 45).^[110] These two reactions were illustrated by various examples with modest to very good yields.

Sonogashira couplings followed by cyclization were well described using palladium catalyst and copper salts as co-catalysts for the synthesis of heterocyclic compounds. Nowadays, domino one-pot reactions with the only use of copper salts were highlighted by the catalyst community. Indeed, they reduce the number of steps of the synthesis and also permit a direct access to the desired compounds. Not long ago, Satyanarayana and co. presented an efficient copper-catalysed intermolecular alkylation between *o*-bromobenzyl tertiary alcohols and terminal aryl acetylenes followed by an intramolecular anti-5-*exo*-dig cyclization (scheme 48).^[114] This protocol leads to the synthesis of 1,3-dihydro-2-benzofurans which are well presented in natural products.^[115] Additional work was recently reported for the synthesis of isobenzofuran-1(3*H*)-ones *via* copper-catalysed cyanation followed by an intramolecular nucleophilic attack using water as a solvent. The desired compounds were obtained in good to excellent yields (scheme 48).^[116] Sekar and co. reported the synthesis of 2-arylbenzo[*b*]furans by coupling *o*-iodophenol and aryl acetylenes (scheme 48).^[117] Sonogashira-type cross-coupling reaction is followed by intramolecular cyclisation.



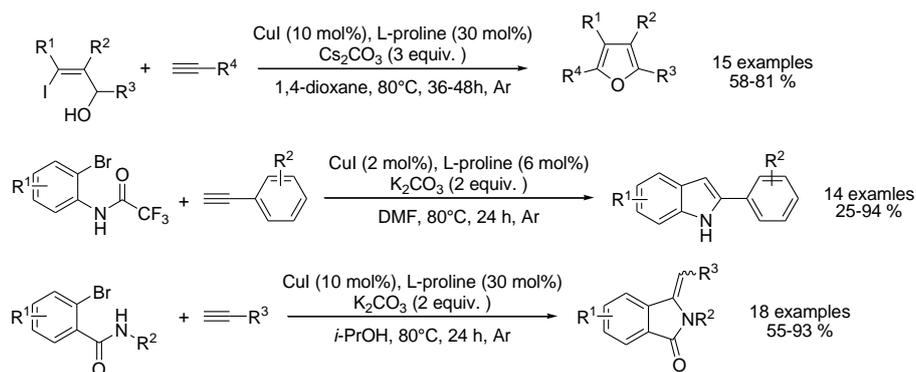
Scheme 48. Synthesis of 1,3-dihydro-2-benzofurans and 2-arylbenzo[*b*]furans *via* domino reaction.

Recently, a general and efficient Cu(I)-mediated cross-coupling between 3-iodoimidazo[1,2-*a*]pyridine-2-carboxylic acid and terminal alkynes, followed by heterocyclization reaction, was developed by Gueiffier and co. under very mild conditions (scheme 49).^[118] This method allows the introduction in one pot of a third ring fused in positions 2 and 3 of the imidazo[1,2-*a*]pyridine core with good yields and total regioselectivity.



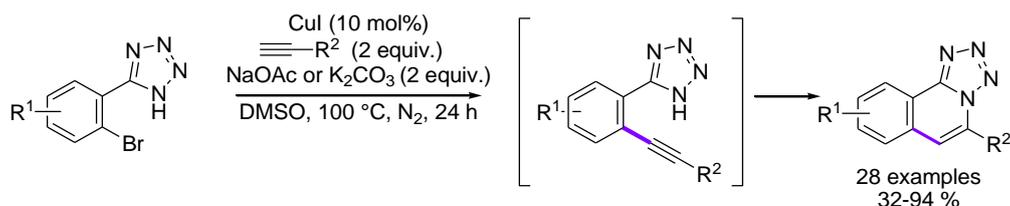
Scheme 49. Cu(I)-mediated cross-coupling affording imidazo[1,2-*a*]pyridine core.

An original and convenient domino route to natural nostoclidines I and II^[119] has been developed using a two-step sequence consisting of a copper-catalysed tandem reaction associated with Suzuki cross-coupling.^[120] The first step consists in a tandem coupling-oxacyclization, occurring in the presence of a catalytic amount of copper iodide and potassium carbonate as base in *N,N*-dimethylformamide at 60 °C for four hours. In these conditions, terminal alkynes and (*E*)-2,3-dihalo-4-methylpen-2-enoic acids formed β -brominated nostoclidines precursors with good yields (scheme 50).



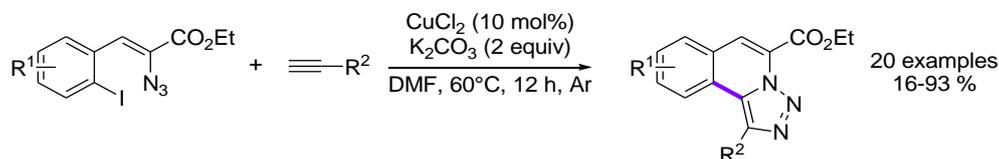
Scheme 52. Synthesis of furan, indole and isoindolin-1-one derivatives *via* domino reaction.

As previously described for indole and benzofurane moieties, 1,5-disubstituted tetrazoles also occurred in natural products and biologically active molecules.^[128] Domino reaction *via* copper-catalysed Sonogashira cross coupling followed by intramolecular addition of the NH from tetrazole group to the internal alkyne leads to the synthesis of tetrazolo[5,1-*a*]isoquinolines (scheme 53).^[129] Utilization of inexpensive copper (I) iodide with a weak base afforded the best result for versatile substitutes of the benzyl ring.



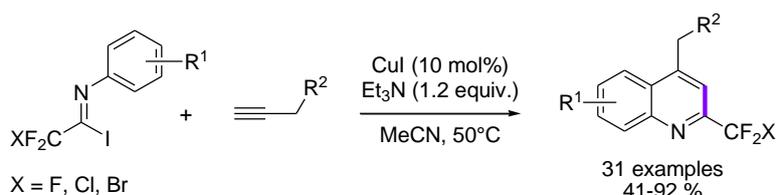
Scheme 53. Copper-catalysed Domino synthesis of tetrazolo[5,1-*a*]isoquinolines.

Liang and co. reported a Sonogashira-type reaction followed by intramolecular [2+3] cycloaddition to prepare 2,3-dihydro-[1,2,3]triazolo[5,1-*a*]isoquinoline (scheme 54).^[130] The coupling between 2-azido-3-(2-iodophenyl)acrylates and terminal alkynes are catalysed by copper chloride in the presence of potassium carbonate as a base in *N,N*-dimethylformamide at 60 °C under an argon atmosphere. No ligand is required for this domino reaction.



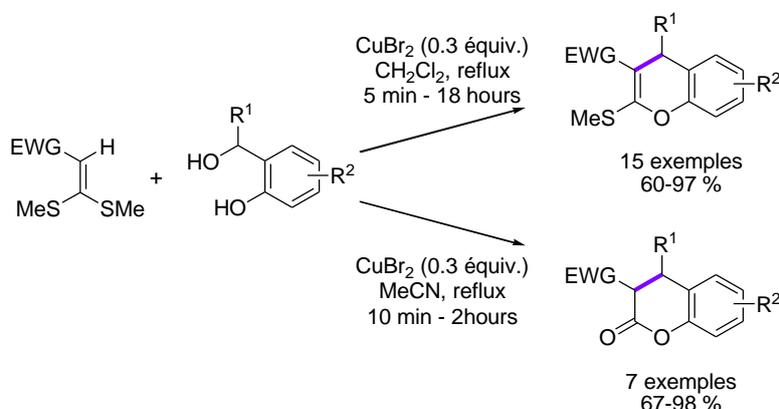
Scheme 54. Synthesis of 2,3-dihydro-[1,2,3]triazolo[5,1-*a*]isoquinoline *via* domino reaction.

Wu and co. described the synthesis of 2-fluoromethylated quinolones *via* a coupling/cyclization sequence.^[131] Copper iodide catalysed alkylation followed by intramolecular cyclisation of fluorinated imidoyl iodides in the presence of trimethylamine in acetonitrile at 50 °C (scheme 55). The desired quinolones were isolated with good yield. Recently, another example of alkylation/cyclisation reaction was reported by Wang and co. for the synthesis of phenanthrenes.^[132]



Scheme 55. Synthesis of 2-fluoromethylated quinolones *via* coupling/cyclization sequence.

Polyfunctionalized 4*H*-chromenes were synthesized from ketene dithioacetals and (2-hydroxymethyl)phenols in the presence of catalytic amount of copper bromide in dichloromethane (scheme 56).^[133] Changing the solvent from dichloromethane to acetonitrile led to obtain dihydrocoumarins instead of 4*H*-chromenes. The domino reaction involves C-C bond formation between ketene dithioacetals and 2-(hydroxymethyl)phenols followed by nucleophilic substitution reaction to lead to 4*H*-chromenes. Hydrolysis of 4*H*-chromenes furnishes thermodynamically stable dihydrocoumarins.

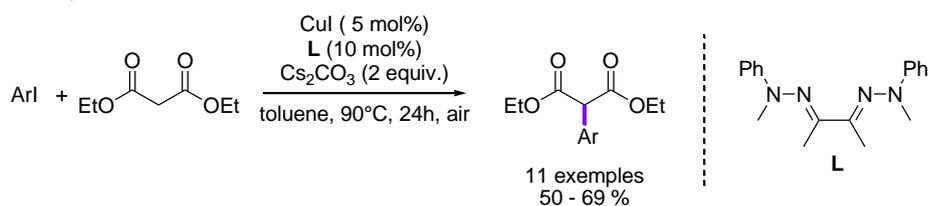


Scheme 56. Synthesis of dihydrocoumarins and 4*H*-chromenes.

7. Other reactions

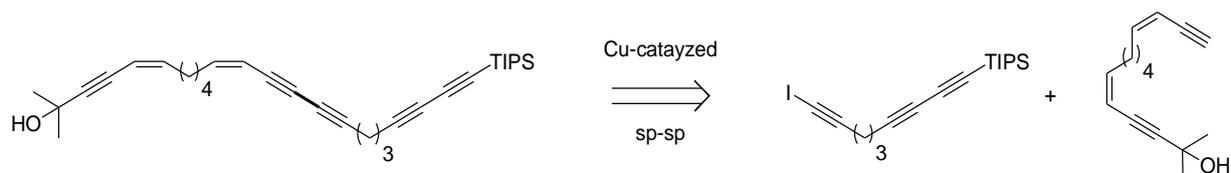
Copper was used in other reaction types, such as Hurtley reaction, alkyne homo- and heterocoupling, deacetylenative cross-coupling reaction or trifluoromethylation reaction. These various couplings are presented in this part.

The Hurtley reaction, described for the first time in 1929, is the older copper-catalysed C(sp³) – C(sp²) bonds coupling reaction. Its major restrictions include harsh reaction conditions at the time, in particular, high temperatures and the uses of strong bases and stoichiometric amounts of copper salts.^[134] Some enhancements have been provided since its initial use. For example, Mino and co. proposed a cross-coupling reaction between aryl iodide and diethylmalonate in the presence of a catalytic amount of copper iodide, hydrazine **L** as ligand, and cesium carbonate as base in toluene at 90 °C (scheme 57).^[135]



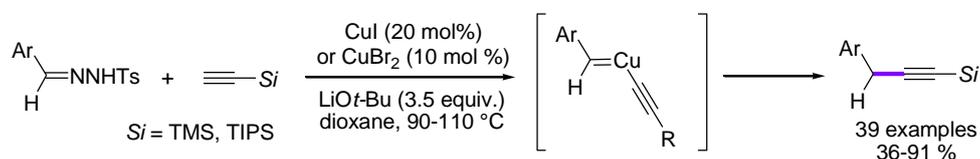
Scheme 57. Hurtley-type reaction.

López and co. envisioned efficient and selective routes to natural and synthetic polyenes and polyenyne. Actually, they focused on marine polyacetylenes Callyberynes A-C (scheme 58).^[136] Starting from the iodotrynes, Callyberyne A can be easily synthesized in two steps. The Cadiot-Chodkiewicz reaction under Alami's optimized conditions led to the polyenyne desired in 60 % yields. Followed by a deprotection step, the marine natural product, Callyberyne A was obtained with only low yield (9%). Other examples of copper-catalysed hetero- and homocoupling of alkynes have been described by Jiang and co.^[137] The reaction proceeds in supercritical carbon dioxide and furnishes desired unsymmetrical or symmetrical diynes with good yields.



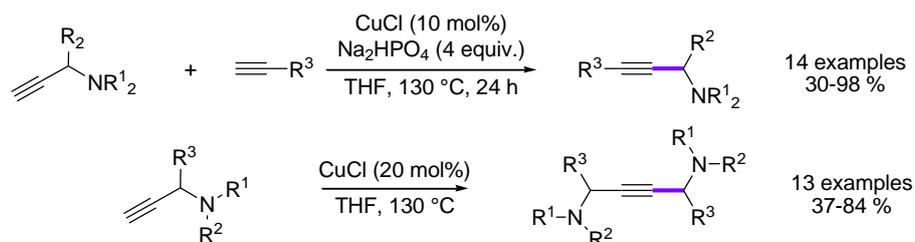
Scheme 58. Access to polyenyne *via* Cadiot-Chodkiewicz reaction.

Since the beginning of the century, different works reported by Wang and co. have emerged for copper-catalysed cross-coupling of *N*-tosylhydrazones with terminal alkynes.^[138] In 2012, they reported copper-catalysed coupling between *N*-tosylhydrazones and trialkylsilylalkynes in the presence of lithium *tert*-butanolate in dioxane (scheme 59).^[139] The key step of the reaction involves a copper(I) carbene migratory insertion process. These conditions involve a cheap copper catalyst and a wide range of functional group compatibility.



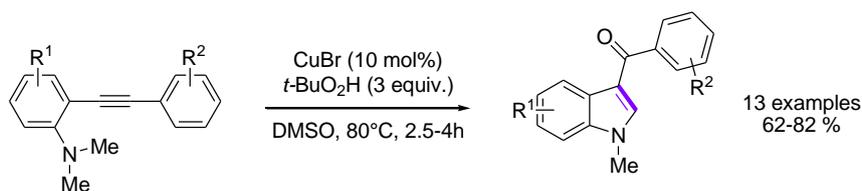
Scheme 59. Copper-catalysed cross-coupling of *N*-tosylhydrazone with terminal alkynes.

In recent years, strategies for activation of C(sp³)-H bonds α to nitrogen have resulted in a variety of reactions. The key for these transformations is the generation of iminium intermediates with assistance from the lone pair of electrons of the α -nitrogen *via* a single-electro transfer mechanism. Nakamura and co. investigated various kinds of C-C coupling reactions with propargylamines.^[140] Recently, copper(I)-catalysed deacetylenative cross-coupling reaction of terminal alkynes with propargylic amines *via* C(sp)-C(sp³) bond cleavage was reported using copper chloride in the presence of sodium hydrogenophosphate as base in tetrahydrofuran at 130°C (scheme 60).^[141] Without a base, propargylamines lead to deacetylenative homocoupling compounds with modest to good yields (scheme 60).^[142]



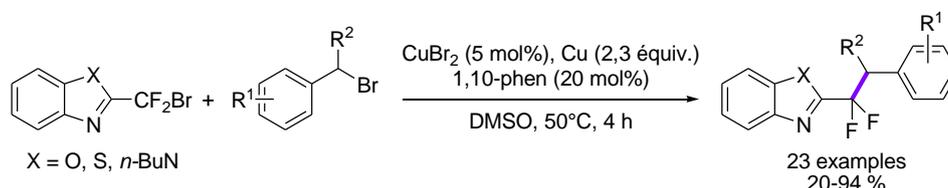
Scheme 60. Deacetylenative heterocoupling and homocoupling of propargylamine.

Patel and co. reported synthesis of 3-aryloindoles from *o*-alkynated *N,N*-dimethylamines.^[143] The reaction involves C-C and C-O formation in the presence of copper bromide as catalyst and *tert*-butylhydroperoxide as oxidant in dimethylsulfoxide at 80 °C (scheme 60).



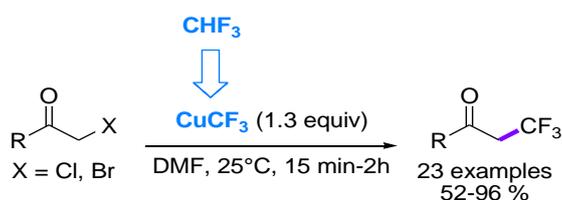
Scheme 61. Synthesis of 3-aryloindoles.

The formation of $\text{CH}_2\text{-CF}_2$ bonds has been developed by Hao and co. through radical C-C cross-coupling *via* two separate single electron transfer processes under the promotion of different copper sources.^[144] In this way, they described direct *gem*-difluoromethylation of a benzylic $\text{C}(\text{sp}^3)\text{-Br}$ using benzo-1,3-azolic(oxa-,thia- or aza-) difluoromethyl bromides (scheme 62).



Scheme 62. Direct *gem*-difluoromethylation of sp^3 -hybridized carbon center.

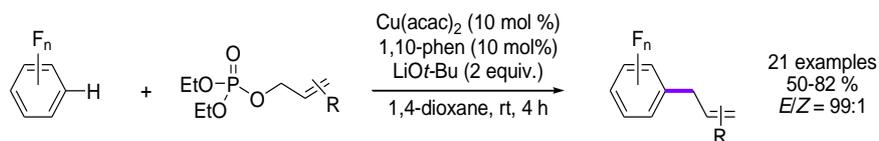
The nucleophilic trifluoromethylation of the C-X (X = Br, Cl) bonds of α -haloketones was promoted by (trifluoromethyl)copper prepared from fluoroform.^[145] The reaction is high-yielding, rapidly and smoothly occurring at ambient temperature, and exhibiting unprecedented functional group tolerance (scheme 63).



Scheme 63. Trifluoromethylation of α -haloketones

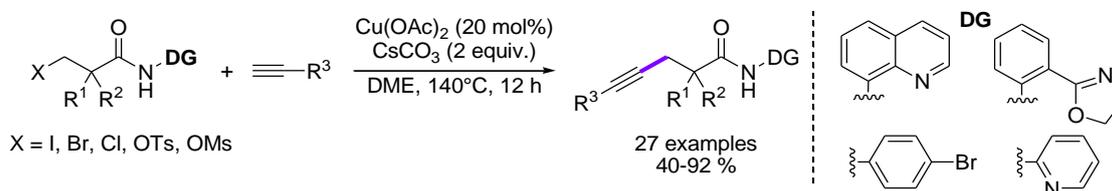
Miura and co. reported direct C-H allylation of polyfluoroarenes with allyl phosphates.^[146] The reaction is catalysed by copper (II) in the presence of 1,10-phenanthroline as ligand and lithium butanolate in

1,4-dioxane at room temperature (scheme 64). The allylarenes are obtained in a stereospecific manner.



Scheme 64. Allylation of polyfluoroarenes with allyl phosphates.

Recently, Shi and co. investigated alkylation of unactivated C(sp³)-X bonds with terminal alkynes.^[147] Internal alkynes were prepared in the presence of copper acetate and cesium carbonate in 1,2-dimethoxyethane (DME) at 140 °C (scheme 65). The copper-catalysed reaction proceeds with the assistance of various amides as directing groups.



Scheme 65. Alkylation of unactivated C(sp³)-X bonds with terminal alkynes.

8. Conclusion

Since the first use of copper to promote C-C bond formation, copper chemistry has been developed as a powerful tool for synthesis. In fact, copper catalysts are very attractive because of their low cost, no toxicity, and high functional group tolerance. Therefore it can be used in a wide field of applications as the synthesis of natural products. Over the past twenty-five years, this chemistry has been expanded as evidenced by the wealth of literature. At the beginning, it was used as co-catalyst then, copper became a full catalyst in Sonogashira- type reactions and decarboxylative cross-coupling reactions. Moreover, it even replaced palladium in some Suzuki- and Negishi- type coupling reactions. Among its various applications in C-C bond formation, copper has been used for C-H functionalization and deshydrogenative cross-coupling. In the interest of atoms economy, these two reactions are a central concern of chemists. Copper allows DCD reactions from a wide variety of substrates, as shown in this review. It was also a catalyst of choice for domino reactions with C-C coupling reaction followed by cyclisation leading to different heterocycles. Many copper catalyzed reactions are performed without ligand which has an economic advantage. However, the association of ligands to the copper-based catalysts could lead to new fields of applications. Copper performs in catalytic cycle in different ways because of its diverse oxidation states and the possibility of radical mechanism. Some mechanism studies allow us to better understand the role of copper in coupling reactions. Understanding and anticipating the mechanisms of copper-catalysed reactions would expand the possibilities of its use. These recent developments accentuate the strong interest for a copper catalyst. Even though numerous works have been reported, optimizations and new applications are still being discovered. If access to molecular diversity and functionality remains a challenge in the contemporary organic synthesis, copper has its place as synthesis tools.

Keywords: Copper catalysed reaction • C-C cross-coupling • Dehydrogenative coupling • Decarboxylative coupling • Domino reaction

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